In claim 44, line 8, please delete "an allergic" and insert therefor, -- a --.

REMARKS

Claims 25-28, 42, and 44 have been amended. Claims 1-44 remain in the case. Reconsideration is respectfully requested.

Applicants affirm the election of Group II claims 10-12, 14-28, 30-39, and 42-44 with traverse. Applicants traverse the restriction requirement for the following reasons: Claims 10-12, 14-28, 30-39 and 42-44 (Group II) are drawn to *Cry j I* protein, peptides thereof and methods of treating or diagnosing sensitivity to Japanese cedar pollen allergen in an individual. Claims 1-9, 13, and 29 (Group I) are drawn to isolated DNA encoding *Cry j I* protein or fragments thereof. The DNA sequence of claims 1-9, 13, and 29 when expressed is the same allergenic protein or peptide of Japanese Cedar pollen of claims 10-12, 14-28, 30-39 and 42-44. Thus, there appears to be a relationship between Groups I and II which precludes them from being termed "independent."

The Examiner has rejected claims 10-12, 14-28, 30-39 and 42-44 under 35 U.S.C. §101. The Examiner states that the claims must recite a degree of purity above and beyond that found in nature. Applicants respectfully submit that the Examiner has misunderstood the use of the term "purified" as recited in the claims. Applicants are not claiming a purified product of nature (i.e. a protein purified from pollen), but are instead claiming the protein *Cry j I* or at least one antigenic fragment thereof which is recombinantly, or synthetically produced. It is clear to one skilled in the art that the recitation of producing the protein in a host cell transformed with a specific nucleic acid sequence in claims 10-12, etc., or producing a protein synthetically would not result in a purified product of nature. Furthermore, page 9 lines 4-10 clearly defines the terms isolated or purified as used in the present specification. Therefore, applicants

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respectfully submit that this rejection has been overcome and respectfully request that it be withdrawn.

The Examiner further compares the presently claimed invention to that disclosed in U.S. Patent No. 4,939,239 to Matsuhashi, and states that in view of Matsuhashi, the present invention does more harm than good. Applicants strongly disagree. Matsuhashi discloses the drawbacks of hyposensitization immunotherapy using an extract of intact cedar pollen allergen. However, despite some of the drawbacks of standard immunotherapy, this method of treating allergy is still considered useful and has been used successfully to treat many allergy patients. The present invention further decreases the possibility of anaphylaxis during immunotherapy and therefore improves the chances that the associated drawbacks of using cedar pollen extract will not occur.

Furthermore, the attendant problems described by Matsuhashi regarding working with whole purified native pollen (i.e. its tendency to absorb on glassware) is not an issue as one skilled in the art is capable of determining which stabilizers, buffers or other pharmaceutical agents would be capable of preventing this problem.

The Examiner further states that the therapeutic uses of the present invention are unpredictable. Applicants respectfully disagree. As described on pages 10 and 11 of the present specification, *Cry j I* protein allergen or fragments thereof of the present invention can be administered for therapeutic purposes such as in standard immunotherapy. As discussed above, although there are certain drawbacks, native protein allergens have been used successfully to treat allergy patients. Therefore, therapy using *Cry j I* of the present invention is not believed to be unpredictable. Additionally, with respect to the peptides of the invention, other investigators have suggested the use of peptidic fragments of a protein for immunotherapy (see e.g., Litwin *et al., Int. Arch. Allergy Appl. Immunol.* **87**:361-366 (1988) and Mucherheide et al., *Cellular Immunology* **50**:340-347 (1980)).

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The informalities noted by the Examiner have been corrected in accordance with the Examiner's request.

The Examiner has objected to the specification and rejected claims 10-12, 14-28, 30-39 and 42-44 under 35 U.S.C. §112. The Examiner states that the specification failed to enable the therapeutic application of the invention. In view of the above discussion, applicants respectfully submit that the specification is enabling for therapeutic use of the present invention.

The Examiner has rejected claims 10-12, 14-18, 25-28, 30, 33, 36-39, and 42-44 under 35 U.S.C. §112, first paragraph.

The Examiner states that claims 10, 11, and 12 are indefinite in the recitation of the term "purified". As used in the present specification and claims, the term "purified" does not refer to purified native pollen protein. The term "purified" is clearly defined on page 9, lines 4-10 of the present specification. Thus, applicants respectfully submit that the Examiner's rejection has been obviated, and accordingly request that it be withdrawn.

The Examiner states that claims 10, 12, 14-18, 32, 33, 36-39, 42-44 are indefinite in the recitation of the phrase "at least one". The Examiner states that amendment of the claims is required to recite distinctly which fragments are being claimed. Applicants respectfully disagree. Applicants are the first to determine the entire nucleic acid sequence which codes for the Japanese cedar pollen allergen *Cry j I*, and the first to disclose the amino acid sequence. Once the entire nucleic acid sequence has been determined and the protein sequence deduced therefrom, any number of fragments of that protein can be produced recombinantly or synthetically. Thus, applicants respectfully submit that they should be entitled to any fragment of *Cry j I* which is produced recombinantly or synthetically as is claimed in the above-mentioned claims. To limit applicants to only particular fragments would be unduly restrictive and not reflect applicants' contribution to the art.

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The Examiner states that claims 25-28 and 42 are indefinite in the recitation of the phrase "capable of modifying." Claims 25-28 and 42 have been amended to positively recite that the antigenic fragments do modify the allergic response of an individual to Japanese cedar pollen.

The Examiner states that claims 30-32 are indefinite in the recitation of the term "reduces". Applicants respectfully submit that it is clear to one skilled in the art that reduction of the allergic response of the individual to Japanese Cedar pollen allergen can be determined by standard clinical procedures (see e.g. Varney et al. *British Medical Journal,* 302: 265-269 (1990).

The Examiner states that claims 38 and 39 are indefinite in the recitation of the phrase "a therapeutically effective amount". As discussed on page 11, lines 21-26 of the specification, and as is well known in the art, therapeutically effective amounts of the compositions of the invention will vary according to a number of factors. It is believed that one skilled in the art would be capable of determining an appropriate therapeutic dosage.

The Examiner states that claim 42 is indefinite in the recitation of the phrase "down regulation". The term "down regulation" is a well known term of art. Applicants respectfully submit that it would be unduly restrictive to limit the present invention to a particular level of down regulation as one skilled in the art would be capable of determining when statistically significant down regulation of the immune system has occurred when using the present invention.

The Examiner states that claim 44 is indefinite in the recitation of the phrase "sufficient quantity". Applicants submit that it is clear to one skilled in the art that the amount of Japanese cedar pollen allergen necessary to provoke a response indicative of sensitivity in accordance with the method of claim 44 will vary depending on a number of factors including the degree of sensitivity of the individual to Japanese cedar pollen,

the age, and the sex of the individual. Applicants submit that one skilled in the art would be capable of determining a sufficient quantity in accordance with claim 44 .

The Examiner states that claims 1-44 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that claimed in copending App. Ser. No. 07/729,134. Applicants respectfully submit that a terminal disclaimer will be filed in due course or one of the cases will be abandoned in order to overcome this rejection.

The Examiner has rejected claims 10-12, 14-20, 23, 26-28, 30-39, and 42-44 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,939,239 to Matsuhashi. Applicants respectfully submit that that the presently claimed invention is not anticipated by or obvious in view of the cited reference for the following reasons.

The Examiner states that Matsuhashi anticipates the invention by disclosing a method of purifying the same cedar pollen allergen as is presently claimed. Applicants respectfully submit that Matsuhashi is purifying native Japanese cedar pollen protein allergen. By contrast, the present invention discloses recombinantly or synthetically produced *Cry j I*, or fragments thereof. It is well known that there are a number of structural differences between the native form of a protein and the recombinantly or synthetically produced non-native form of that same protein.

Furthermore, without the disclosure by Matsuhashi of the entire nucleic acid sequence or deduced amino acid sequence of the Japanese cedar pollen allergen, there is no way of knowing which of the allergens form Japanese cedar pollen Matsuhashi and co-workers have purified.

Therefore, Matsuhashi does not teach every element of claims 10-12, 14-20, 23, 26-28, 30-39, and 42-44 as is required for anticipation. Accordingly, applicants respectfully request that the rejection of the claims under this section be withdrawn.

Applicants further submit that the presently claimed invention is not obvious in view of the cited Matsuhashi reference for the following reasons.

Matsuhashi teaches away from the presently claimed invention in that Matsuhashi is limited to using an allergen-pollulan conjugate to effect hyposensitization. Matsuhashi does not teach, suggest, or disclose, that synthetically or recombinantly produced *Cry j I* allergen, or a fragment thereof, or much less unconjugated recombinantly or synthetically produced *Cry j I* allergen or a fragment thereof, may be used directly to modify the immune response of an individual sensitive to Japanese cedar pollen. Therefore, Applicants respectfully submit that the above claims are not obvious in view of Matsuhashi.

The Examiner has rejected claims 21, 22, and 24 under 35 U.S.C. §102 (b) and 35 U.S.C §103 as anticipated or obvious in view of Matsuhashi. Applicants respectfully disagree for the following reasons:

As discussed above, Matsuhashi does not suggest or disclose the use of antigenic fragments of Japanese cedar pollen allergen, much less *Cry j I*, and therefore, does not teach every element of claims 21, 22, and 24 as required for anticipation.

The Examiner further states that since Matsuhashi discloses protein degradation, one skilled in the art would be capable of producing antigenic fragments which do not bind IgE. Applicants respectfully disagree. There is no suggestion in Matsuhashi that would lead one to use protein degradation to produce antigenic fragments. Furthermore, as discussed on page 13, line 29 to page 14, line 29, the structural information of the *Cry j I* protein is necessary in order to design fragments (peptides) capable of modifying the immune response to Japanese cedar pollen. Moreover, it would be almost impossible to produce antigenic fragments using an enzyme degradation procedure as disclosed in Matsuhashi for the following reasons:

First, it would be almost impossible to reproduce the exact same peptides in every degradation experiment even if the same enzyme degradation scheme is used each time. Second, it is very difficult to purify peptides from the heterogeneous mixture of peptides which results from an enzyme degradation procedure.

Therefore, applicants respectfully submit that it would not be obvious in view of Matsuhashi to produce antigenic fragments of *Cry j I*.

In view of the amendments to the claims and the above remarks, Applicants respectfully submit that all claims now patentably distinguish over the prior art of record. Accordingly, allowance of all claims is respectfully requested. If the Examiner has any questions regarding this amendment or this application, he is cordially invited to telephone the undersigned attorney.

Respectfully submitted,

By _____

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